IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: LARCHE *et al*

Serial No.10/809,689

File: 25 March 2004

For: METHODS AND COMPOSITIONS FOR DESENSITISATION

DECLARATION

I, Dr Mark Larché do hereby declare and state as follows:

1. I am a British subject of the Department of Medicine, McMaster University, 1200 Main Street West, Hamilton Ontario, L8N 3Z5, Canada. I presently have the positions of Professor (Department of Medicine McMaster University), Canada Research Chair in Allergy & Immune Tolerance, GSK/McMaster University Chair in Lung Immunology and Honorary Professional Research Fellow, Imperial College, London, UK. I have been working in the field of peptide immunotherapy since 1995. My publications in this field are shown in the attached annex.

2. I am one of the inventors named for US Patent Application 10/809,689. I understand that the US Patent Office Examiner has objected that the desensitisation method described in the claims of this patent application lacks enablement, written description and novelty. I have been asked to comment on the Examiner=s objections.

3. The work described in US Patent Application No 10/809,689 concerns desensitisation of subjects against specific polypeptide allergens by administration of peptides derived from the same allergen. The peptides have the property of inducing restriction to a MHC class II molecule in the patient (i.e. have a functional T-cell epitope). The peptides are also able to induce a late phase response in those individuals, which underlies the ability of the peptides to desensitise against the whole allergen.

4. I believe that the documents cited by the Examiner to assert the unpredictability of peptide

immunotherapy in the art do not support a conclusion that the claimed methods would not allow for desensitisation against the allergens listed in claim 1.

I understand that the methods require inhibiting of an allergic reaction, and do not require complete abolishment of allergic responses. I believe that the findings made in the field of peptide immunotherapy support the conclusion that peptides can be used to inhibit allergic response against whole allergen.

In regard to the cited document Francis *et al*, which I co-authored, the discussion of cat peptide vaccine clinical trials at page 538 mentioned by the Examiner does not detract from the generally positive conclusions established in this review of the field of peptide immunotherapy as a whole. The Examiner mentions individual studies e.g. Pene *et al* which gave poor results for cat peptide vaccines. In fact, as described in Francis et al., a statistically significant improvement in bronchial allergen tolerance was detected within certain groups. Poor results in individual studies could be due to any number of factors, including deficiencies in the methodology used in a given trial. Evidence of some negative results needs to be read in the general context of the other more successful studies in the field. For example, as stated at page 538, right column, first paragraph of Francis *et al*, Oldfield *et al* (ref 25) reported a study with successful effects in reducing responses to Feld1 using cat peptides. Norman *et al* [ref 22] discussed at page 538, fourth paragraph of Francis *et al* also reports improvement of allergic symptoms following cat peptide immunotherapy. Although I understand that use of Fel d1 peptides is not being claimed nevertheless the data presented in US Patent Application No. 10/809,689 in relation to these peptides reinforces the conclusion that overall, at the priority date, peptide immunotherapy with Fel d1 was feasible.

Importantly, as discussed further at page 539 of Francis *et al*, second paragraph, investigations into the use of peptide immunotherapy for tolerisation against another allergen, bee venom also resulted in positive findings. In particular, studies by Muller *et al* [ref 33] and Tarzi *et al* [ref 34] both show that peptide immunotherapy is predictable in that positive findings for a cat allergen could be replicated for a bee allergen. The overall conclusions of Francis *et al*, as summarised at page 541, conclusions section, are that as a whole, peptide immunotherapy is a predictable art. I therefore believe that it is credible that the claimed methods could be used to reduce allergic responses to any of the specific allergens named in claim 1.

5. The Examiner also cites Kinnunen *et al* to argue that altered forms of the native peptide sequence of an allergen do not predictably cause desensitisation. In particular, the Examiner notes a discussion of earlier results obtained in clinical trial using variant peptides derived from an autoimmune antigen, MBP for treatment of multiple sclerosis, an autoimmune disease. The results obtained in that study are not directly relevant to the claimed methods which relate to allergen therapy, specifically desensitisation against the specific allergens listed in claim 1. The mechanisms underlying T-cell responses in autoimmune disease and allergy are distinct. It cannot be extrapolated from a negative result in autoimmune disease that altered peptides would not be effective agents for treatment of allergy therapy. This caveat is noted by the authors of Kinnunen *et al* at page 6, left column, third paragraph. They state that there is no particular reason to suspect that altered peptides would be ineffective in desensitising against allergens, and that in fact therapy of allergy with altered peptides is likely to be a predictable art. As such Kinnunen *et al* does not allow the conclusion that altered peptides are not suitable in general for treatment of allergy.

Furthermore, the claims require restriction to an MHC class II molecule by the peptide referred to and induction of a late phase response. Thus, any altered peptides that do not have these functional properties, and thus might not lead to desensitisation are not being claimed. I therefore believe that it is credible that altered peptides could be used in methods of desensitisation against the listed allergens.

6. I understand that the Examiner is also of the opinion that the application does not provide adequate information on which particular peptides can be used to desensitise in the claimed methods. However, abundant sequence information is provided in US patent application 10/809,689. Sequence information is provided for the allergens listed in claim 1. This information would readily allow preparation of synthetic peptides from 5 to 50 amino acids in length as claimed. Furthermore, synthetic peptides could readily be subjected to the routine experimentation of the type described in Example 6 so as to identify whether they are suitable for desensitisation. Therefore, the disclosure of the application does provide the claimed peptides because it provides sequence information from which the sequences of the peptides could be identified by routine means and using the teaching in Example 6.

7. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such wilful false statements may jeopardize the validity of this declaration, the patent application, or any patents issuing thereon.

Signed _____ Dr Mark Larché

This 17th Day of February 2009.